Neuroanatomical correlates of cognition in advanced Parkinson's disease in absence of dementia

Undergraduate Research Thesis

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Abstract

Introduction Investigation of neuroanatomical correlates of cognition in Parkinson's disease (PD) has been confined to patients with earlier diagnosis. This study examined the relationship between brain structure and neuropsychological performance in multiple cognitive domains in a non-demented sample characterized by longstanding disease duration and severe motor symptoms.

Methods Volumetric T1-weighted magnetic resonance imaging (MRI) and neuropsychological pre-surgical data were collected on a consecutive sample of 41 patients being considered for deep brain stimulation (DBS). Voxel-based morphometry (VBM) was utilized to examine the relationship between grey matter (GM) density and executive functioning, processing speed, verbal fluency, and memory.

Results Reduced GM density across multiple brain regions was associated with poorer executive functioning performance. This diffuse pattern encompassed Heschl's gyrus and the parahippocampal gyrus of the temporal lobe, olfactory bulb and rolandic operculum of the frontal lobe, calcarine fissure and lingual gyrus of the occipital lobe, and the thalamus. No significant associations were found between GM density and performance on measures of processing speed, fluency, or memory.

Conclusion The association of such a broad anatomical network with executive functioning may explain patterns of executive dysfunction demonstrated in PD. Given the extent of brain regions associated with executive function, we hypothesize that this aspect of cognition may be uniquely vulnerable to diffuse pathology. Thus, this may lend understanding as to why executive dysfunction is a predominant impairment in PD, even in individuals without dementia.

Key Words: Parkinson's disease, neuroanatomical correlates, cognition, executive functioning, neuropsychology, voxel-based morphometry (VBM)

Introduction

Cognitive dysfunction in Parkinson's disease (PD) is a primary predictor of poor prognosis.(1) Beyond the impact of motor impairment on disability, cognitive deficits are significantly associated with functional decline(2) and reduced quality of life.(3) It is estimated that 24-31% of PD patients have dementia.(4) Even for those who do not meet criteria for a dementia diagnosis, cognitive deficits have been demonstrated across a range of cognitive domains. Prevalence of cognitive deficits has been shown to increase with disease duration and severity.(5)

One possible mechanism for cognitive deficits evidenced in PD is cerebral atrophy. Studies have consistently demonstrated widespread cortical atrophy for PD patients with dementia(6-12) in addition to atrophy of subcortical areas including the hippocampus,(7, 11-13) limbic structures,(7, 10, 12) and caudate.(11, 12) Even more notable are studies that have demonstrated atrophy in the brains of individuals with PD compared to healthy controls. Significant reductions in grey matter volume have been shown in the frontal and temporal lobes,(6, 8, 14) parietal and occipital lobes,(8) hippocampus and anterior cingulate.(13) Such neuroanatomical differences have been evidenced even in early, untreated PD populations.(6, 8, 14) These findings can contribute to current understandings of the cognitive pathophysiology of PD.

While loss of dopaminergic neurons in the basal ganglia is the accepted pathophysiological mechanism for motor dysfunction in PD, there is a lack of consistency in relating differential patterns of brain structure to PD nonmotor symptoms.(15) It has been proposed that differences in structural brain volume may represent the biological substrates for nonmotor symptoms in PD, particularly cognitive deficits.

While previous research has examined this question in the context of categorical disease conditions (e.g., dementia vs. mild cognitive impairment vs. no dementia), few studies have assessed neuroanatomical correlates of performance in specific cognitive domains within the spectrum of normal cognitive functioning that exists in the PD population.(12, 16, 17, 18) Furthermore, these investigations have focused exclusively on patients with early-stage disease. To our knowledge, we are the first group to examine the relationship between brain structure and specific cognitive domains in a non-demented PD population characterized by longstanding disease duration and severe motor symptoms, who were being considered (and later underwent) deep brain stimulation (DBS).

Methods

Subjects

Archival pre-surgical data from a consecutive sample of 56 individuals with PD who underwent DBS between 2009 and 2012 were used for this study. Preoperative assessment included neurological examination, neuropsychological evaluation, and neuroimaging. Fifteen subjects were excluded from analyses due to poor magnetic resonance imaging (MRI) scan quality. Analyses were conducted on the remaining 41 subjects. Patient data were obtained from the Center for Neuromodulation at the Ohio State University (OSU) Wexner Medical Center. This study was approved by the university's Institutional Review Board.

Assessments

Subjects with idiopathic PD with a history of problematic motor fluctuations, medication refractory tremor, or medication intolerance as determined by evaluation by a Movement Disorder Neurologist were referred for DBS consideration. PD diagnosis was confirmed by a Neurological Specialist with Movement Disorder training using the UK Brain Bank criteria for Parkinson's Disease.(19) Motor symptom severity was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS-III) off levodopa medication. Total medication dose for PD was calculated in levodopa equivalents using previously published methods.(20)

The neuropsychological battery was a comprehensive evaluation across several cognitive domains. Composite scores were created for analyses, as follows: Executive Functioning – Trails B and Stroop Color Word; Processing Speed – Trails A, Stroop Word, and Stroop Color; Fluency – Animal Naming and Controlled Oral Word Association Test (FAS); and Memory - California Verbal Learning Test-Long Delay Free Recall (CVLT-II). Raw scores on these measures were converted to demographically corrected T-scores; composite scores were calculated by averaging T-scores of the measures within each domain. A notable strength of the composite scores is that the executive functioning composite reflects a purer metric of cognitive flexibility, as the processing speed composite accounts for the more rudimentary attentional and speeded components of these tasks. Clinical interview and neuropsychological evaluation confirmed the absence of dementia, according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR).(21) Depression was assessed with the Beck Depression Inventory (BDI-II) or the Geriatric Depression Scale (GDS), as clinically indicated.

Neuroimaging and Data Analysis

MRI Acquisition

Volumetric contrast T1-weighted MRIs were acquired from scanners at the OSU Martha Morehouse Plaza and Wexner Medical Center. Of the 41 patients, 16 were imaged on 1.5-Tesla machines: a 1.5-T GE Medical Systems Signa HDxt (n = 8) and a 1.5-T Siemens Espree (n = 8), whereas 25 patients were imaged on 3.0-Tesla scanners: a 3-T Siemens Verio (n = 17) and 3-T Philips Medical Systems Achieva (n = 8). MRI scanner parameters for both 1.5-Tesla scanners were as follows: TR (repetition time) = 12.0 ms; TE (echo time) = 4.2 ms; TI (inversion time) = 600 ms; acquisition matrix 512 × 512; ST (slice thickness) = 1.2 mm; and flip angle = 15˚. The 3-T Siemens Verio parameters were: TR = 6.5; TE = 2.5; acquisition matrix 320 × 320; ST = 0.9; and flip angle = 10.5˚. The 3-T Philips Medical Systems Achieva parameters were: TR = 7.5; TE = 3.7; acquisition matrix 240 × 240; ST = 2.0; and flip angle = 8˚. All images were obtained axially in uncompressed Digital Imaging and Communications in Medicine format and converted into Nifti format for processing and analysis.

MRI Data Preprocessing

MRIs were visually rated to ensure scan quality. Of the original 56, 15 scans were omitted due to excessive noise and movement. Thus, analyses were conducted on the remaining 41 subjects. Scans were corrected for radiofrequency inhomogeneity using the Statistical Parametric Mapping toolbox (SPM8, Wellcome Department of Cognitive

Neurology, http://www.fil.ion.ucl.ac.uk/spm). Skull-stripping was performed using an in-house Matlab 8.2 (MathWorks) script to prevent extrabrain voxels from being classified as grey matter.

Voxel-Based Morphometry

Voxel-based morphometry (VBM) refers to the voxel-wise comparisons of regional grey matter volume and density.(22) In particular, unmodulated VBM (without brain region scaling) was performed, representing differences in GM concentration or "relative density" rather than volumetric differences. Each patient's preoperative brain scan underwent a procedure of segmentation (into grey matter, white matter, and cerebrospinal fluid) and joint normalization (to standard space) using the SPM8 Matlab software suite. Brains were normalized to custom older adult templates(23) in MNI space to equate for differences in overall head size between subjects. Images were then smoothed using a 10mm Gaussian kernel to suppress noise and effects due to residual differences in gyral anatomy. The VBM processing steps are depicted in Figure 1.

Statistical Analysis

To determine whether a patient's baseline cognition relates to extent of grey matter atrophy, individual voxel-wise multiple regressions were performed correlating grey matter density to each of the four cognitive domain scores. Confounding factors with a potential to influence grey matter density (age and disease duration) were included as covariates in the model. Determination as to which of four hospital scanners was used for preoperative imaging was primarily random (based on scanner availability), except for a few participants being excluded from scanning on the 3.0-T Philips magnet due to requiring anesthesia for severe movements. Orthogonal contrast coding was utilized to assess the effect of different field strengths (1.5-T vs. 3.0-T) and scanner types (1.5-T GE vs. 1.5-T Siemens; 3.0-T Philips vs. 3.0-T Siemens) to determine whether inter- and intra-scanner groups differentially affected GM classification. Systematic differences in grey matter classification were observed between the two field strengths and within the two 3.0-T scanner types, but not within the two 1.5-T scanner types. Thus, two dummy coded dichotomous nuisance covariates were included in the final model to account for the effect of scanner type on GM classification.

Focal changes in grey matter were identified using paired t tests at individual 2-mm isometric voxels (i.e., voxel-wise statistics). Voxel-wise beta coefficient t statistics for each domain of cognitive performance were thresholded at $\alpha_{uncorrected} = 0.05$ ($t = \pm 2.0211$). More spatially diffuse changes in grey matter were quantified by testing for increases over a significant number of adjacent voxels (i.e., cluster-wise statistics). Correction for family-wise error by use of nonparametric permutation procedures(24) (n = 1,000 iterations) determined the threshold for significant cluster size (n = 199,766 voxels).

Results

The sample consisted of 41 participants, all of whom were Caucasian and predominantly male. Demographic and clinical characteristics of the sample are presented in Table 1.

Cluster-wise analysis revealed that GM density was inversely associated with age (cluster size = 379,353 voxels, p=.01) and positively associated with the composite executive function measure (cluster size = 217,375 voxels, p<.05) (Figure 2). The significant cluster for executive function represents a diffuse pattern of cerebral atrophy that includes areas within frontal, parietal, occipital, and temporal cortices; insular and cingulate cortices; subcortical areas including the amygdala, hippocampus, basal ganglia, and thalamus; and cerebellum. Specifically, the most salient regions included Heschl's gyrus (mean β= .0029), thalamus (mean β= .0027), olfactory bulb (mean β= .0022), calcarine fissure (mean β= .0021), rolandic operculum (mean β= .0017), lingual gyrus (mean β= .0017) and parahippocampal gyrus (mean β= .0016). Locations of greatest salience are presented in Table 2. No significant associations or trends were observed between GM density and the composite scores for processing speed, fluency, or memory (p>.34). Disease duration was also not predictive of GM density (p=.59).

Discussion

Poorer executive function was associated with diminished grey matter density across diffuse brain regions encompassing areas within all four lobes; insular and cingulate cortices; subcortical areas including striatum, limbic structures, and thalamus; and cerebellum. No significant associations were demonstrated between GM density and processing speed, fluency, or memory.

Previous studies that have examined the neuroanatomical correlates of executive function in individuals with Parkinson's disease without dementia have yielded varied and inconsistent results. Camicioli et al.(16) found an association between a composite index of executive function (similarly comprised of Stroop, Trails, and digit ordering) and grey matter atrophy in the caudate, middle temporal gyri, precuneus, and cerebellum. Mak et al.(17) demonstrated significant correlations between insular and middle temporal atrophy and executive dysfunction as measured by the Frontal Assessment Battery and clock drawing test. Performance on other less conventional measures thought to reflect executive function, such as Raven Colored Progressive Matrices, has been associated with grey matter density in the dorsolateral prefrontal cortex and the parahippocampal gyrus.(12) Inconsistencies in these studies are likely attributable to differences in sample characteristics and cognitive measures.

Furthermore, previous research that has investigated grey matter integrity and performance on specific domains of cognition in individuals with PD without dementia has exclusively focused on patients with early-stage disease. To our knowledge, this is the first study investigating the neuroanatomical correlates of cognitive functioning in individuals with longstanding Parkinson's disease and severe motor impairment in absence of dementia. Our patient sample of DBS qualifiers provided a unique cohort of PD patients in regard to their motor and cognitive symptom presentation and the medically refractory nature of their disease process. It is conceivable that this patient sample may be unique in regard to cognitive resiliency and/or neuropathology.

The diffuse anatomical associations with executive dysfunction demonstrated in this study are consistent with patterns found not only in PD populations, but also in other neurological disorders, including corticobasal syndrome,(25) Alzheimer's disease, and Mild Cognitive Impairment.(26) Other researchers have hypothesized that the diffuse anatomical associations with executive function reflect other components (e.g., motor,

visual) inherent in neuropsychological measures. However, our study accounted for this by covarying out processing speed (composite of Trails A, Stroop Color, and Stroop Word) in our regression model to achieve a "purer" metric of the mental flexibility component of executive functioning. That the anatomical correlates with executive function in this study remained diffuse provides evidence that a large cortico-striatal-thalamic-cerebellar network is involved in executive function, and, more specifically, with mental flexibility. We hypothesize that, in the context of PD, the involvement of a broad anatomical network may explain why executive dysfunction is a predominant impairment in PD, even in those without dementia. Since executive functioning is associated with a vast number of brain regions, pathology in any of these areas could theoretically result in executive deficits. The association of such a large network with executive functioning may also explain why such deficits are often present even at early stages of PD and tend to worsen with disease progression.(27)

As mentioned above, previous research on individuals with early-stage disease has revealed associations between executive functioning and frontal, temporal, caudate, and cerebellar regions. Our study examined a population with longer disease duration and demonstrated a broader pattern of neuroanatomical associations with executive function. Such findings are consistent with recent theories regarding disease progression and network decentralization. In a longitudinal study of brain network topology in PD using magnetoencephalography,(28) progressive decreases of local clustering in multiple frequency bands and progressively decentralized, less-integrated network configurations were demonstrated during both motor and cognitive tasks. Additionally, a recent fMRI study of altered resting state brain networks in PD, independent of cognitive variables, identified decreases in local and global functional connectivity as well as various compensatory increases in the sensorimotor module connectedness.(29) Since our modality for GM analysis of cognition demonstrates the diffuse clustering and decentralization in areas of decreased functional connectivity, our findings support the notion that as disease progresses, increased and seemingly more "random" network recruitment subserves specific compensatory cognitive functions (e.g., executive functioning).

One limitation of this study is that these results were generated from a highly specific patient sample (PD patients being considered for DBS) and therefore are not generalizable to all non-demented individuals with PD, even those with severe motor impairment and long disease duration. The possibility of selection bias cannot be ruled out given that various psychosocial factors may influence referral for DBS and/or a person's willingness to consider DBS. Furthermore, our sample was entirely Caucasian, limiting generalizability to other ethnic groups. Additionally, the cross-sectional nature of this study precludes causal inference that atrophy of the aforementioned brain regions yields declines in executive functioning. Longitudinal research is needed to further investigate the cognitive and neuropathological trajectories of individuals with Parkinson's disease.

In summary, this study expanded upon previous research investigating the neuroanatomical correlates of cognitive functioning in PD by examining DBS candidates who are non-demented, but characterized by long disease duration and severe motor impairment. Correlating GM density with executive functioning revealed a diffuse, global pattern of neuroanatomical regions. We hypothesize that these findings, supporting a

large brain network for executive functioning may lend understanding to the predominance of executive deficits in PD, even in individuals who are not globally cognitively impaired.

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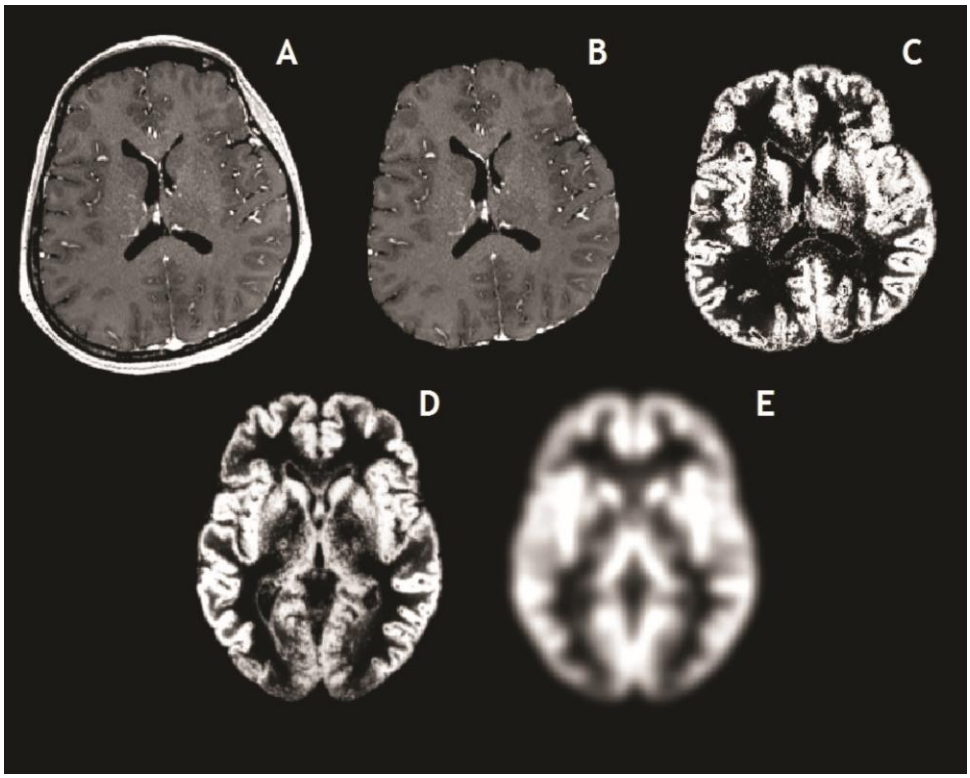
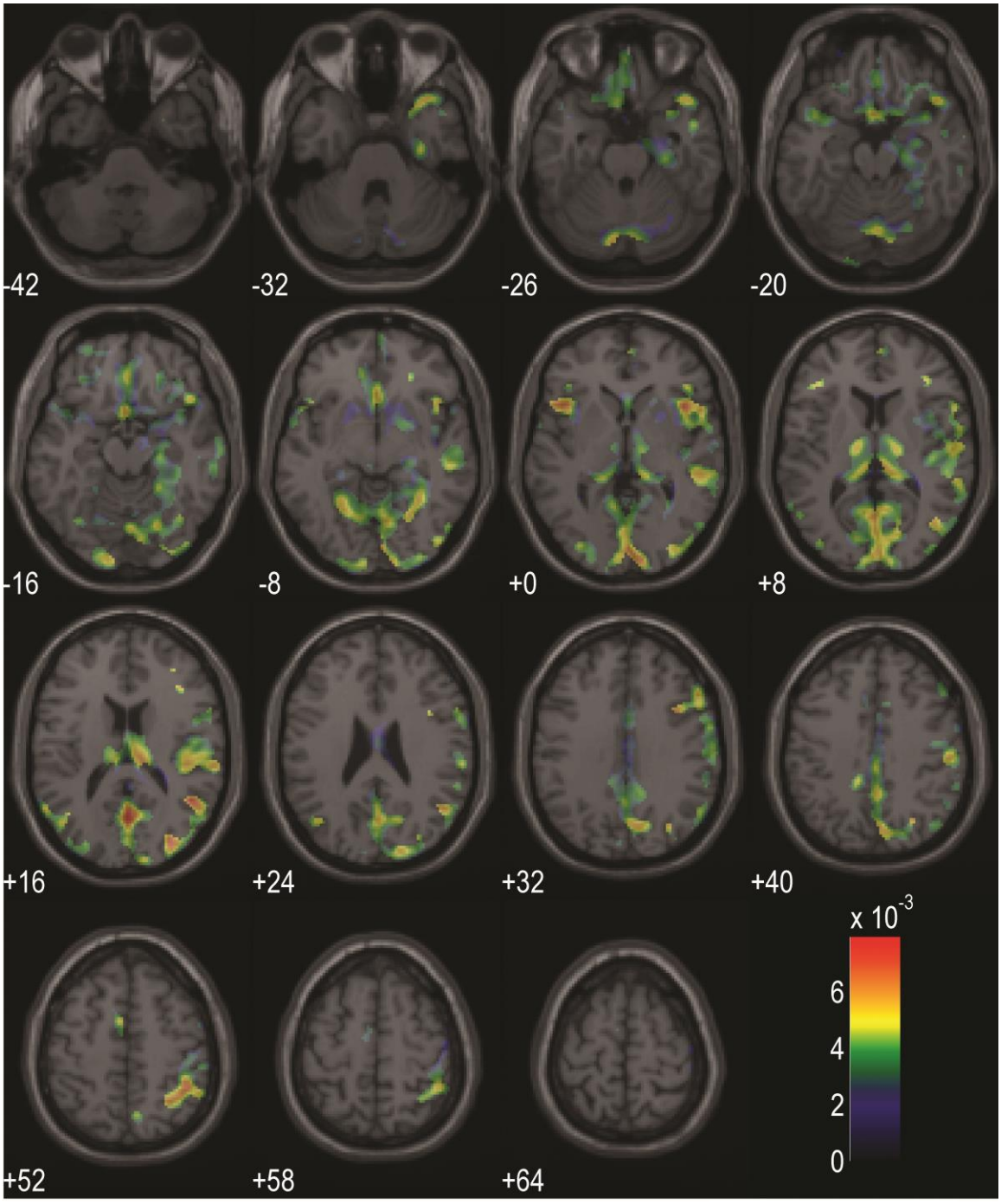
Figures

Figure 1 VBM processing steps for one subject.



(A) Original T1 contrast-weighted image (B) After skull-stripping and inhomogeneity correction (C) Segmented in native space (D) After joint segmentation and normalization to custom older adult templates (E) Smoothed with a 10mm Gaussian kernel to suppress noise and effects due to residual differences in gyral anatomy.

Figure 2 Cluster-wise analysis of GM density and executive functioning in patients with longstanding PD without dementia.



Areas of higher beta value (red) represent a greater association. Images are oriented in axial view following neurological convention (i.e., right hemisphere of brain corresponds to right side of image).

Tables

Table 1 Sample demographics and clinical characteristics (*n*=41).

Table 1 Sample demographics and clinical characteristics (*n*=41)

	Mean ± SD	Range
Age	60.6 ± 9.7	39 - 81
Gender (M:F)	34:7	
Handedness (R:L)	34:7	
Education	14.4 ± 3.2	9 - 23
PD Duration, years	14.1 ± 6.5	6 - 40
Unified Parkinson's Disease Rating Scale (UPDRS III)	44.2 ± 12.6	26 - 72
Levodopa-equivalent dose, mg	825 ± 623	0 - 2500
Executive Function		
Trails B	35.1 ± 13.1	7 - 59
Stroop Color-Word	35.5 ± 11.2	19 - 66
Processing Speed		
Trails A	38.6 ± 12.0	12 - 60
Stroop Word	38.1 ± 10.6	19 - 61
Stroop Color	33.6 ± 10.8	19 - 63
Fluency		
Animal Naming	43.8 ± 11.7	19 - 69
Verbal Fluency (FAS)	41.9 ± 12.5	21 - 73
Memory		
California Verbal Learning Test Long-Delay Free Recall (CVLT-LDFR)	43.3 ± 12.8	17 - 77
Beck Depression Inventory-II (BDI-II) (*n*=30)	10.9 ± 6.9	0 - 32
Geriatric Depression Scale (GDS) (*n*=8)	7.3 ± 4.8	1 - 14

Note: All values for neuropsychological tests are reported as T-scores.

Table 2 Location and MNI coordinates of most salient regions

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Location	Mean β	MNI Coordinates		
		x	*y*	*z*
Heschl_R	0.00288836	46	-24	14
Thalamus_R	0.002716485	10	-26	14
Olfactory_R	0.00215577	2	22	-6
Calcarine_L	0.002128369	0	-66	14
Olfactory_L	0.002065491	-2	12	-14
Thalamus_L	0.002012251	-8	-28	12
Lingual_L	0.001728793	-2	-66	8
Rolandic_Oper_R	0.001713462	54	-20	12
Calcarine_R	0.001688665	2	-66	16
Parietal_Inf_R	0.001632348	44	-46	54
ParaHippocampal_R	0.001603022	32	-16	-30
Cuneus_R	0.001582233	6	-74	34
Rectus_L	0.001446529	0	36	-16
Temporal_Pole_Sup_R	0.001445966	34	20	-32
Lingual_R	0.001373193	22	-66	-10
Insula_R	0.001327323	44	14	0
Occipital_Inf_R	0.001325408	34	-88	-2
Frontal_Inf_Oper_R	0.001208333	44	16	2
Hippocampus_R	0.001202587	14	-32	10
Temporal_Mid_R	0.001193843	46	-54	14

MNI – Montreal Neurological Institute